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A division of the American Chemical Society

Dr. Matthew J. Toussant
Vice President, Editorial Operations
mtoussant@cas.org

January 15, 2004

Anthony M. Insogna, Esq.
JONES DAY
1155 Avenue of the Americas
New York, New York 10036-2711

Subject: CAS On-line Abstracts and Indexing with CAS Registry Numbers

Dear Mr. Insogna:

Thank you for your questions and exhibits concerning the interpretation of the indexing for the CAS record 110:185177.

At the outset, I want to be certain that you understand that the compound anthra[1,9-cd]pyrazol-6(2H)-one which has CAS Registry Number (CAS RN)129-56-6 was ***not*** indexed by the CAS analysts and this compound was not represented by CAS in its abstract record as being disclosed or studied in the original article.

Anthra[1,9-cd]pyrazol-6(2H)-one was not part of the abstract record by CAS, rather this online abstract discloses ***only*** derivatives of this substance, as represented by the index entry shown as "129-56-6D, Anthra[1,9-cd]pyrazol-6(2H)-one, derivs.". I write to clarify the indexing procedures used by CAS so that the reader may better understand and correctly interpret the information which this particular abstract sets forth.

In general, CAS RNs are used to describe specific substances, and in some cases substances generically, by reference to a core moiety such as a monomer of a polymer, or to derivatives of a substance by the use of a "D" as described in more detail below.

Specifically, CAS uses a "D" at the end of CAS RNs in situations where the CAS indexing analyst has determined that it is useful to have an index entry that refers to the compounds disclosed by the source publication as derivatives of a moiety or specific compound having a CAS RN. In such cases, even though the analyst has determined that the substance represented by the CAS RN is ***not specifically described*** in the reference to be indexed, the analyst may describe the group of compounds disclosed in the published article by reference to derivatives of a certain CAS registered compound. This is shown in CAS records as a CAS RN with an appended "D" (for derivatives) (*See* CAS public documentation regarding CAS RNs with "D", attached as my Exhibit A).

In the case of the index entry for CAS document 110:185177, the index entry of "129-56-6D, Anthra[1,9-cd]pyrazol-6(2H)-one, derivs." indicates that many compounds with an anthrapyrazolone core moiety were shown and described in the source publication (A copy of this index entry from the CAPLUS database and a copy of CAS Volume 110:185177 are attached as Exhibit B). The ***lack of index entry*** for 129-56-6 as plain (*i.e.*, no appended "D")

indicates that this specific compound is ***not*** described in the reference being indexed (*i.e.*, the source publication) nor is it described *per se* in the abstract.

The basis of this index entry with the appended "D" (*i.e.*, 129-56-6D), entered into the CAS database for the public on 26 May 1989 (original CAS abstract published in print on 22 May 1989), is most likely due to the generic representation shown on p. 207 of the source publication, vol. 6 Bioactive Molecules (1988) (attached as Exhibit C). Indeed, this generic representation does not encompass anthra[1,9-cd]pyrazol-6(2H)-one itself.

I note that the entry in question (*i.e.*, attached as Exhibit D) sets forth the structure of anthra[1,9-cd]pyrazol-6(2H)-one and CAS RN 129-56-6 in the display of the search results. This may have led to some confusion on your part or that of others who look at this display. Despite the manner in which this search result is displayed, this substance is not specifically disclosed in the on-line CAS abstract record. This on-line entry was retrieved only because it discloses derivatives of the compound being searched (*i.e.*, CAS RN 129-56-6). The content of the on-line record is actually that which is disclosed in Exhibit B. Any additional information in the display of the CAS record which was printed (*i.e.*, Exhibit D) is a result of the on-line user's actions in displaying the record. For example, the on-line entry for CAS document 110:185177 contains a hyperlink in "CAS RN 129-56-6D" which, upon being selected, will result in the display of CAS RN 129-56-6 (*see* Exhibit E).

This hyperlink feature is intended to aid the researcher and should not be interpreted as being part of the disclosure of the on-line abstract. I offer my apologies if the manner in which this hyperlinked information is displayed led to a misunderstanding that 129-56-6 (anthra[1,9-cd]pyrazol-6(2H)-one) was indexed in the CAS abstract record. It was not.

I hope that this letter clarifies any confusion.

Sincerely,

Matthew J. Toussant, Ph.D.
Vice President, Editorial Operations
Chemical Abstracts Services (CAS)

Attachments

Exhibit A

THE CA CAplus/CAOLD FILES DATABASE DESCRIPTION

May 1996

In Europe
STN International
c/o FIZ Karlsruhe
Postfach 2465
76012 Karlsruhe
Federal Republic of Germany
Phone: (+49) 7247/808-555
Telex: 17724710+
Telefax: (+49) 7247/808-131
STNmail: HLPDESKK

In Japan
STN International
c/o The Japan Information Center of Science and Technology (JICST)
P.O. Box 2, Kojimachi
Tokyo 102-91 Japan
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STNmail: HLPDESKT

In North America
STN International
c/o CAS
P.O. Box 3012
Columbus, Ohio 43210 U.S.A.
Phone: (614) 447-3731
Telex: 6842086 chmab
Telefax: (614) 447-3751
STNmail: HLPDESKC

CAS Registry Numbers may appear in the CA File records with the suffix P, D, or DP.

```
=> e 622-40-2/bi
E1            2      622-39-9DP/BI
E2           17      622-39-9P/BI
E3          356 --> 622-40-2/BI
E4           17      622-40-2D/BI
E5            6      622-40-2DP/BI
E6           31      622-40-2P/BI
E7          219      622-42-4/BI
E8           31      622-42-4P/BI
E9            2      622-43-5/BI
E10           2      622-43-5P/BI
E11         123      622-44-6/BI
E12           1      622-44-6D/BI
```

The letter P indicates that the document deals with the preparation of the substance. CAS Registry Numbers from all document records in the CA File from 1967 to the present have been so analyzed.

NOTE

The letter D appended to a particular CAS Registry Number means that the document contains information about a generic or nonspecific derivative of the substance identified by that CAS Registry Number. Some examples of nonspecific derivatives are: alkyl esters or polychlorinated derivatives. The suffix DP indicates preparation of a nonspecific derivative. CAS Registry Numbers with D and DP are present in the CA File from the beginning of the 10th Colective Index period, CA volume 86 (1977).

CAS Registry Numbers appended by P, D, or DP are automatically searched whenever CAS Registry Numbers are crossed over from the Registry File or input directly.

You may limit the scope of the search by appending a D, P, or DP to individual CAS Registry Numbers or adding a slash (/) and the desired suffix to the L-number Registry answer set.

Search Term	Retrieval
622-40-2	622-40-2 622-40-2P 622-40-2D 622-40-2DP
622-40-2P	622-40-2P 622-40-2DP
622-40-2D	622-40-2D 622-40-2DP
622-40-2DP	622-40-2DP

Exhibit B

L3 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2004 ACS on STN
Full Text
AN 1989:185177 CAPLUS
DN **110:185177**
ED Entered STN: 26 May 1989
TI Design, tumor biology, and biochemical pharmacology of anthrapyrazoles
AU Showalter, H. D. Hollis; Werbel, Leslie M.; Leopold, Wilbur R.; Fry, David W.; Klohs, Wayne D.; Jackson, Robert C.
CS Dep. Chem., Warner-Lambert/Parke-Davis Co., Ann Arbor, MI, 48105, USA
SO Bioactive Molecules (1988), 6(Anthracycline Anthracenedione-Based Anticancer Agents), 201-43
CODEN: BMOLEY; ISSN: 0921-0687
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review with 63 refs.
ST review anthrapyrazole deriv antitumor pharmacol
IT Neoplasm inhibitors
(anthrapyrazoles as, pharmacol. of)
IT 129-56-6D, Anthra[1,9-cd]pyrazol-6(2H)-one, derivs.
RL: BIOL (Biological study)
(antitumor effects and pharmacol. of)

NOTE

VOLUME 110 CODEN: CHABA8 110(21) 1-814 (1989) NUMBER 21
ISSN: 0009-2258

CHEMICAL ABSTRACTS®

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Exhibit B

MAY 22, 1989

tested in the treatment of acute laminitis. Thrombosis, which frequently occurs in the corium of the foot, may be controlled by administration of anticoagulants such as heparin. Alpha-receptor blocking agents such as phenoxybenzamine have been used to improve the peripheral blood flow. The use of these drugs and that of anti-inflammatory agents during the onset of acute laminits is discussed.

110: 185158p **Antitumor natural products isolated from marine organisms.** Kitagawa, Isao; Kobayashi, Motomasa (Pharm. Coll., Osaka Univ., Osaka, Japan). *Gan to Kagaku Ryoho* 1989, 16(1), 1-8 (Japan). A review with 28 refs., on the antitumor natural products, e.g., peptides, polyethers, alkaloids, prostanoids, etc., from marine organisms (animal invertebrate, algae, etc.).

110: 185159q **Calcium antagonism and ACE inhibition: two outstandingly effective means of interference with cardiovascular calcium overload, high blood pressure, and arteriosclerosis in spontaneously hypertensive rats.** Fleckenstein, A.; Fleckenstein-Gruen, G.; Frey, M.; Zorn, J. (Physiol. Inst., Univ. Freiburg, D 7800 Freiburg, Fed. Rep. Ger.). *Am. J. Hypertens.* 1989, 2(3, Pt. 1), 194-204 (Eng). A review with 36 refs.

110: 185160h **Diuretics.** Levine, Sherman D. (Albert Einstein Coll. Med., Bronx, NY USA). *Med. Clin. North Am.* 1989, 73(2), 271-82 (Eng). A review with 31 refs. on diuretics. Topics discussed include sites of action of diuretics and consequent patterns of electrolyte excretion, selected issues in diuretic therapy, use of diuretics in specific clin. settings and new directions in diuretic physiol.

110: 185161j **Angiotensin-converting enzyme inhibitors in heart failure.** Boerk, Mark; Charlap, Shlomo; Frishman, William H. (Dep. Med., Long Island Coll. Hosp., Brooklyn, NY USA). *Med. Clin. North Am.* 1989, 73(2), 315-38 (Eng). A review with 151 refs. discussing angiotensin-converting enzyme inhibitors in heat failure treatment.

110: 185162k **Calcium antagonists and heart failure.** Charlap, Shlomo; Frishman, William H. (SUNY Health Sci. Cent., Brooklyn, NY USA). *Med. Clin. North Am.* 1989, 73(2), 339-59 (Eng). A review with 76 refs. discussing the mechanisms by which the calcium antagonists can influence cardiac function, current clin. experience regarding the use of there drugs in patients with left ventricular dysfunction, and recommendations as to the use of these agents in patients with heart failure.

110: 185163m **Disposition of cardiovascular drugs in the elderly.** Greenblatt, David J. (Sch. Med. Chief, Tufts Univ., Boston, MA USA). *Med. Clin. North Am.* 1989, 73(2), 487-94 (Eng). A review with 43 refs. on the disposition of cardiovascular drugs in the elderly. Topics discussed include interpreting pharmacokinetic changes in old age, pharmacodynamic changes, propranolol in the elderly and complicating factors in pharmacogeriatric studies.

110: 185164n **Effects of Wuweiji and its constituents on biochemical and pharmacological function of liver.** Liu, Gengtao (Inst. Mater. Med., Chin. Acad. Med. Sci., Beijing, Peop. Rep. China). *Shengli Kexue Jinzhan* 1988, 19(3), 197-203 (Ch). A review, with 15 refs., discussing the action mechanism of Wuweiji and its constituents against liver injury.

110: 185165p **Antiviral agents and AIDS.** Hanc, Oldrich (Ceskoslov. Farm., 11000 Prague, Czech.). *Cesk. Farm.* 1989, 38(1), 29-35 (Czech). A review with 122 refs.

110: 185166q **Agents with antituberculous effects. III. Thiazolidine derivatives.** Waisser, K.; Kucharcik, P.; Celadnik, M. (Farm. Fak., Univ. Karlovy, Hradec Kralove, Czech.). *Cesk. Farm.* 1989, 38(1), 36-42 (Czech). A review with 73 refs.

110: 185167r **Prevention of amphotericin B nephrotoxicity: the effect of salt loading and flucytosine.** Heidemann, H. (Med. Klin., Christian-Albrechts-Univ., D-2300 Kiel, Fed. Rep. Ger.). *Mycoses* 1988, 31(Suppl. 2), 39-44 (Eng). A review with 13 refs.

110: 185168s **Inhibition of angiotensin coverting enzyme (ACE) in plasma and tissues: studies ex vivo after administration of ACE inhibitors.** Johnston, Colin I.; Mendelsohn, Fredrick A. O.; Cubela, Rose B.; Jackson, Bruce; Kohzuki, Masahiro; Fabris, Bruno (Dep. Med., Univ. Melbourne, Heidelberg, 3084 Australia). *J. Hypertens.* 1988, 6(Suppl 3), S17-S22 (Eng). A review with 33 refs. of the inhibition of angiotensin-converting enzyme (ACE) in various tissues (blood plasma, brain, aorta, lung, kidney, and testis) by ACE inhibitors. The techniques of radioligand inhibitor binding and in vitro autoradiog. in detg. tissue ACE inhibition are emphasized.

110: 185169t **Cephalosporins: a basic overview and clinical perspective. Part II: Focus on the third-generation cephalosporins.** Willett, Michael S.; Absher, Randall K. (Marion Lab., Kansas City, MO USA). *J. Pharm. Technol.* 1989, 5(1), 14-22 (Eng). A review with 49 refs. on third-generation ephalosporins. Topics discussed include antimicrobial spectrum of activity, pharmacokinetic and dosing considerations and clin. uses.

110: 185170m **Molecular mimicry and drugs.** Burgen, Arnold V. (Darwin Coll., Cambridge, UK CB3 9EU). *Int. Congr. Ser. - Excerpta Med.* 1988, 823(Mol. Mimicry Health Dis.), 3-12 (Eng). A review with 12 refs. examg. structure-activity relationships in pharmacol.

110: 185171n **Comments on method and theory in drug discrimination: a potpourri of problems, perplexities, and possibilities.** Holloway, Frank A.; Gauvin, David V. (Health Sci. Cent., Univ. Oklahoma, Oklahoma City, OK 73910-3000 USA). *Drug Dev. Res.* 1989, 16(2-3-4), 195-207 (Eng). A review with 55 refs.

110: 185172p **Subjectively experienced cannabis effects in animals.** Jaerbe, Torbjoern U. C.; Hiltunen, Arto J.; Mechoulam, Raphael (Dep. Psychol., Univ. Uppsala, S-751 48 Uppsala, Swed.). *Drug Dev. Res.* 1989, 16(2-3-4), 385-93 (Eng). A review with 45

110: 185173q **Morpholinyl anthracyclines.** Acton, Edward M.; Wasserman, K.; Newman, Robert A. (Cancer Cent., Univ. Texas Syst., Houston, TX 77030 USA). *Bioact. Mol.* 1988, 6(Anthracycline Anthracenedione-Based Anticancer Agents), 55-101 (Eng). A review with 81 refs. on prepn., structure-activity relations, mechanisms of action, preclin. testing, and toxicity of antitumor morpholinyl anthracyclines.

110: 185174r **Antitumor anthracycline antibiotics from microbial origins.** Oki, Toshikazu (Tokyo Res. Cent., Briston-Myers Res. Inst., Ltd., Tokyo, Japan 153). *Bioact. Mol.* 1988, 6(Anthracycline Anthracenedione-Based Anticancer Agents), 103-27 (Eng). A review with 71 refs.

110: 185175s **Metal anthracycline and anthracenedione complexes as a new class of anticancer agents.** Garnier-Suillerot, Arlette (Lab. Chim. Bioinorg., Univ. Paris Nord, 93012 Bobigny, Fr.). *Bioact. Mol.* 1988, 6(Anthracycline Anthracenedione-Based Anticancer Agents), 129-61 (Eng). A review with 84 refs.

110: 185176t **Biochemical pharmacology and tumor biology of mitoxantrone and ametantrone.** Durr, Frederick E. (Chemother. Res. Dep., Am. Cyanamid Co., Pearl River, NY 10905 USA). *Bioact. Mol.* 1988, 6(Anthracycline Anthracenedione-Based Anticancer Agents), 163-200 (Eng). A review with 81 refs.

110: 185177u **Design, tumor biology, and biochemical pharmacology of anthrapyrazoles.** Showalter, H. D. Hollis; Werbel, Leslie M.; Leopold, Wilbur R.; Fry, David W.; Klohs, Wayne D.; Jackson, Robert C. (Dep. Chem., Warner-Lambert/Parke-Davis Co., Ann Arbor, MI 48105 USA). *Bioact. Mol.* 1988, 6(Anthracycline Anthracenedione-Based Anticancer Agents), 201-43 (Eng). A review with 63 refs.

110: 185178v **X-ray di[illegible] gonucleotide complexe** CNR, 00016 Monteroto[illegible] 6(Anthracycline Anthrac[illegible] (Eng). A review with 73

110: 185179w **Binding the interaction of antitu[illegible] with double stranded** Bernard (Lab. Biochim. Fr.). *Bioact. Mol.* 198[illegible] Anticancer Agents), 371-400 (Eng). A review with 73 refs.

110: 185180q **Molecular pharmacology of anthracenedione-based anticancer agents.** Reszka, Krzysztof; Kolodziejczyk, Pawel; Hartley, John A.; Wilson, W. David; Lown, J. William (Dep. Chem., Univ. Alberta, Edmonton, AB Can. T6G 2G2). *Bioact. Mol.* 1988, 6(Anthracycline Anthracenedione-Based Anticancer Agents), 401-45 (Eng). A review with 124 refs. examg. the binding of anthracenediones to DNA, enzymic activation of anthracenedione and anthrapyrazole antitumor agents, and photosensitization by these agents.

110: 185181r **DNA topoisomerase II as intracellular target in anthracycline treatment of cancer.** Potmesil, Milan (Sch. Med., New York Univ., New York, NY 10016 USA). *Bioact. Mol.* 1988, 6(Anthracycline Anthracenedione-Based Anticancer Agents), 447-74 (Eng). A review with 113 refs. Topics considered include: the function and regulation of DNA topoisomerases; topoisomerase interactions with chemotherapeutic agents; topoisomerase-related mechanisms of drug resistance; and applications to anthracycline development.

110: 185182s **Biochemical mechanisms of tumor cell kill by the anthracyclines.** Myers, Charles E.; Mimnaugh, Edward G.; Yeh, Grace C.; Sinha, Birnadra K. (Clin. Pharmacol. Branch, Natl. Cancer Inst., Bethesda, MD 20892 USA). *Bioact. Mol.* 1988, 6(Anthracycline Anthracenedione-Based Anticancer Agents), 527-69 (Eng). A review, with 133 refs., on anthracycline mechanisms of action, metabolic activation by redn., DNA intercalation, and membrane effects.

110: 185183t **Mechanisms of anthracycline resistance.** Kessel, David H. (Sch. Med., Wayne State Univ., Detroit, MI 48201 USA). *Bioact. Mol.* 1988, 6(Anthracycline Anthracenedione-Based Anticancer Agents), 599-627 (Eng). A review with 147 refs. Different modes of anthracycline resistance are discussed, including multidrug-resistance. Several resistance determinants are considered: transport systems, enzymes involved in drug detoxification, and repair of drug-induced cellular damage. Prospects for reversal of drug resistance modes are also described as are results of drug analog development programs.

110: 185184u **Menogaril: pharmacology and phase I/II clinical trails.** McGovren, J. Patrick; Adams, Wade J.; Earhart, Robert H. (Upjohn Co., Kalamazoo, MI 49001 USA). *Bioact. Mol.* 1988, 6(Anthracycline Anthracenedione-Based Anticancer Agents), 629-66 (Eng). A review, with 51 refs., on the pharmacol. and phase I/II clin. trials with anthracycline antitumor agent menogaril.

110: 185185v **Anthracyclines as inducers of tumor cell differentiation.** Casazza, Anna Maria (Pharm. Res. Dev. Div., Bristol Myers Co., Wallingford, CT 06492-7660 USA). *Bioact. Mol.* 1988, 6(Anthracycline Anthracenedione-Based Anticancer Agents), 715-34 (Eng). A review, with 45 refs., on the present knowledge on anthracyclines with respect to cell differentiation, and the possible relevance that this effect has in contributing to the clin. efficacy of these antibiotics.

110: 185186w **Action mechanism of oral blood sugar-lowering agents.** Kaku, Kohei; Kaneko, Toshio (Med. Sch., Yamaguchi Univ., Yamaguchi, Japan). *Shindan to Chiryo* 1989, 77(1), 76-82 (Japan). A review, with 27 refs., discussing the action mechanism of sulfonylureas and other oral hypoglycemics.

NOTE

Exhibit B

Exhibit C

09642557

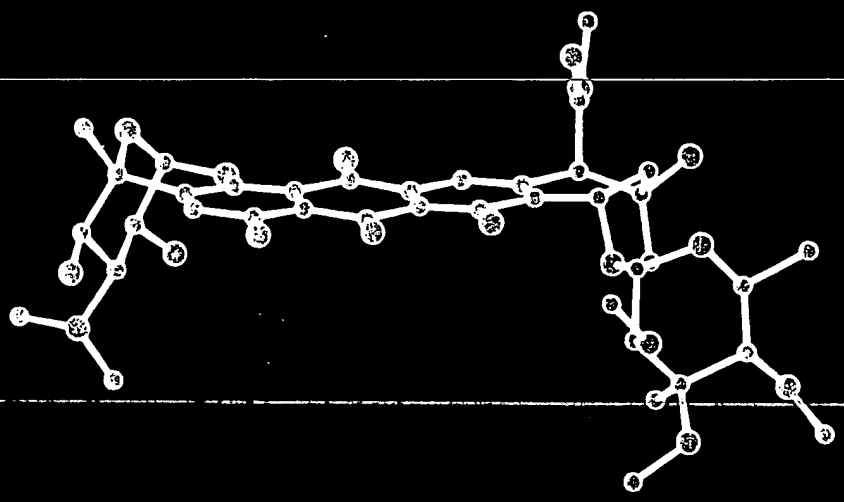
Matt Jousant

9380
57

bioactive molecules

volume 6

ANTHRACYCLINE AND ANTHRACENEDIONE - BASED ANTICANCER AGENTS



EDITED BY

Exhibit C

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Chapter VI

0-444-87275-2 43pp 1988

Design, Tumor Biology, and Biochemical Pharmacology of Anthrapyrazoles

H.D. Hollis Showalter, Leslie M. Werbel, Wilbur R. Leopold, David W. Fry, Wayne D. Klohs, and Robert C. Jackson

(82) Dep. Chem.
(84) Warner-Lambert/Parke-Davis Co.
(86) Ann Arbor (90) MI
(92) US
(94) 48105

Exhibit C

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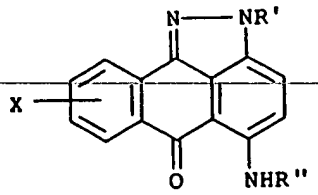
TABLE I

ANTHRAPYRAZOLES SELECTED FOR ADVANCED STUDIES



Compound		R'	R''	X
1		$-(CH_2)_2N(CH_2CH_3)_2$	$-(CH_2)_2NH(CH_2)_2OH$	7,10-$(OH)_2$
2		$-(CH_2)_2OH$	$-(CH_2)_2NH(CH_2)_2OH$	7,10-$(OH)_2$
3		$-(CH_2)_2NH(CH_2)_2OH$	$-(CH_2)_2NH(CH_2)_2OH$	H
4		$-(CH_2)_2N(CH_2CH_3)_2$	$-(CH_2)_2NH_2$	7,10-$(OH)_2$
5		$-(CH_2)_2N(CH_3)_2$	$-(CH_2)_2NH(CH_2)_2OH$	7,10-$(OH)_2$
6		$-(CH_2)_2OH$	$-(CH_2)_2N(CH_3)_2$	7,10-$(OH)_2$
7		$-(CH_2)_2NH(CH_2)_2OH$	$-(CH_2)_2NH_2$	7,10-$(OH)_2$
8	(CI-942)	$-(CH_2)_2NH(CH_2)_2OH$	$-(CH_2)_3NH_2$	7,10-$(OH)_2$
9		$-(CH_2)_2NH(CH_2)_2OH$	$-(CH_2)_2NH(CH_2)_2N(CH_3)_2$	7,10-$(OH)_2$
10		$-(CH_2)_2NH(CH_2)_2N(CH_3)_2$	$-(CH_2)_2NH(CH_2)_2OH$	7,10-$(OH)_2$
11		$-(CH_2)_2NH_2$	$-(CH_2)_2NH(CH_2)_2OH$	7,10-$(OH)_2$
12		$-CH_2CH(OH)CH_2OH$	$-(CH_2)_2NH(CH_2)_2OH$	7,10-$(OH)_2$
13		$-(CH_2)_3N(CH_3)_2$	$-(CH_2)_2NH_2$	7,10-$(OH)_2$
14		$-(CH_2)_2NH(CH_2)_2OH$	$-(CH_2)_2N(CH_2CH_2OH)_2$	7,10-$(OH)_2$
15	(CI-937)	$-(CH_2)_2NH(CH_2)_2OH$	$-(CH_2)_2NHCH_3$	7,10-$(OH)_2$
16		$-(CH_2)_3NH_2$	$-(CH_2)_2NH(CH_2)_2OH$	7,10-$(OH)_2$
17	(CI-941)	$-(CH_2)_2NH(CH_2)_2OH$	$-(CH_2)_2NH(CH_2)_2OH$	7-OH
18		$-(CH_2)_2NH(CH_2)_2OH$	$-(CH_2)_2NH(CH_2)_2OH$	7,8,10-$(OH)_3$
19		$-(CH_2)_2NH(CH_2)_2OH$	$-(CH_2)_2NHCH_3$	7-OH
20		$-(CH_2)_2NH(CH_2)_2OH$	$-(CH_2)_2NHCH_3$	7,8,10-$(OH)_3$
21		$-(CH_2)_2NH_2$	$-(CH_2)_2NHCH_3$	7,10-$(OH)_2$
22		$-(CH_2)_2NH(CH_2)_2OH$	$-(CH_2)_2NH(CH_2)_2OH$	7,10-$(OH)_2$
23		$-(CH_2)_2NH(CH_2)_2OH$	$-(CH_2)_2NH(CH_2)_2OH$	10-OH

09642557

Wilbur R.; Fry, David W.; Klohs, Wayne D.; Jackson, Robert C.

CORPORATE SOURCE: Dep. Chem., Warner-Lambert/Parke-Davis Co., Ann Arbor, MI, 48105, USA

SOURCE: Bioact. Mol. (1988), 6(Anthracycline Anthracenedione-Based Anticancer Agents), 201-43
CODEN: BMOLEY; ISSN: 0921-0687

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

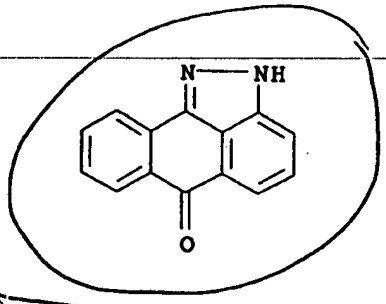
AB A review with 63 refs.

IT **129-56-6D**, Anthra[1,9-cd]pyrazol-6(2H)-one, derivs.
RL: BIOL (Biological study)
(antitumor effects and pharmacol. of)

RN 129-56-6 CAPLUS

CN Anthra[1,9-cd]pyrazol-6(2H)-one (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)

Exhibit D



L4 ANSWER 17 OF 71 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1989:175123 CAPLUS

DOCUMENT NUMBER: 110:175123

TITLE: Identification by NMR and mass spectroscopy of the by-products formed during the synthesis of the red vat dye 1,1'-diethyl-(3,3'-bianthra[1,9-c,d]pyrazole)-6,6'(1H,1'H)-dione

AUTHOR(S): Havlickova, Libuse; Kolonicny, Alois; Lycka, Antonin; Jirman, Josef; Kolb, Ivan

CORPORATE SOURCE: Res. Inst. Org. Synth., Pardubice-Rybitvi, 532 18, Czech.

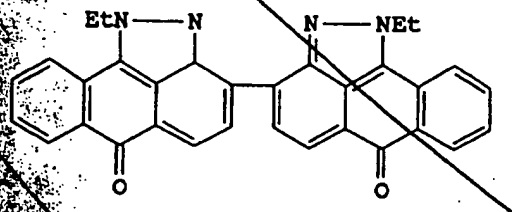
SOURCE: Dyes Pigm. (1989), Volume Date 1988, 10(1), 1-11
CODEN: DYPIDX; ISSN: 0143-7208

DOCUMENT TYPE: Journal

LANGUAGE: English

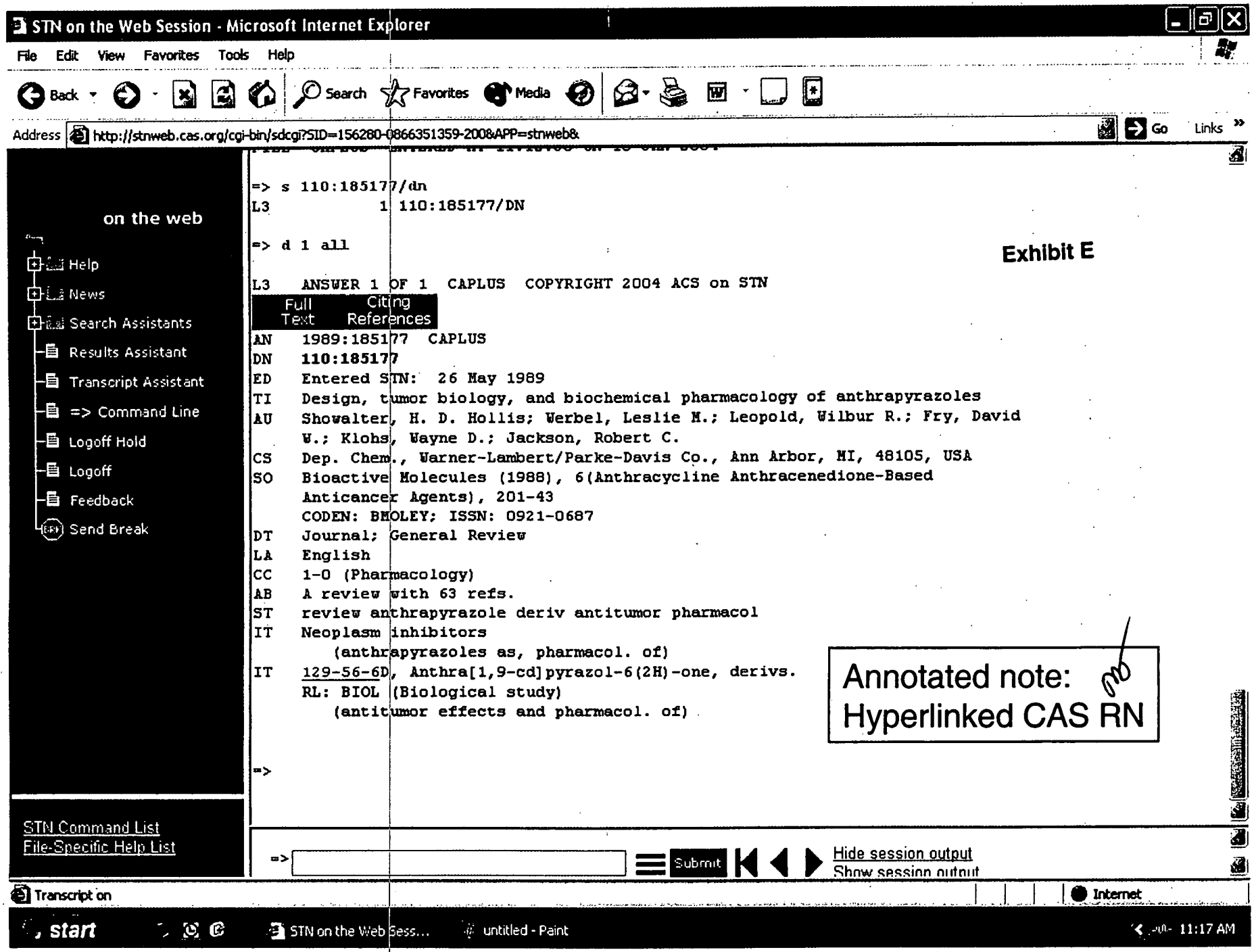
OTHER SOURCE(S): CASREACT 110:175123

GI



I

AB The bis-ethylation of (3,3'-bianthra[1,9-c,d]pyrazole)-6,6'-dione, i.e. bispyrazoloanthrone, gave the red vat dye 1,1'-diethyl-(3,3'-bianthra[1,9-c,d]pyrazole)-6,6'(1H,1'H)-dione (I), together with an orange isomer with Et groups in the 1,2'-positions and a yellow isomer having Et groups in


STN on the Web Session - Microsoft Internet Explorer
File Edit View Favorites Tools Help
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Address http://stnweb.cas.org/cgi-bin/sdcgi?SID=156280-0866351359-200&APP=stnweb&
Go Links
on the web
Help
News
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Results Assistant
Transcript Assistant
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Logoff
Feedback
Send Break
=> s 110:185177/dn
L3 1 110:185177/DN
=> d 1 all
Exhibit E
L3 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2004 ACS on STN
Full Text
Citing References
AN 1989:185177 CAPLUS
DN 110:185177
ED Entered STN: 26 May 1989
TI Design, tumor biology, and biochemical pharmacology of anthrapyrazoles
AU Showalter, H. D. Hollis; Werbel, Leslie M.; Leopold, Wilbur R.; Fry, David W.; Klohs, Wayne D.; Jackson, Robert C.
CS Dep. Chem., Warner-Lambert/Parke-Davis Co., Ann Arbor, MI, 48105, USA
SO Bioactive Molecules (1988), 6(Anthracycline Anthracenedione-Based Anticancer Agents), 201-43
CODEN: BMOLEY; ISSN: 0921-0687
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review with 63 refs.
ST review anthrapyrazole deriv antitumor pharmacol
IT Neoplasm inhibitors
(anthrapyrazoles as, pharmacol. of)
IT 129-56-6D, Anthra[1,9-cd]pyrazol-6(2H)-one, derivs.
RL: BIOL (Biological study)
(antitumor effects and pharmacol. of)
Annotated note:
Hyperlinked CAS RN
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STN Command List
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Express Mail No.: EV 335 860 034 US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Bennett et al.	Confirmation No.: 6892
Application No.: 09/642,557	Group Art Unit: 1626
Filed: August 18, 2000	Examiner: Wright, S.
For: PYRAZOLOANTHRONE AND DERIVATIVES THEREOF AS JNK INHIBITORS AND COMPOSITIONS AND METHODS RELATED THERETO	Attorney Docket No.: 10624-046-999

SUPPLEMENTAL REPLY TO FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.113

Commissioner for Patents
P.O. Box 1450
Mail Stop AF
Alexandria, VA 22313-1450

Sir:

Applicants thank Examiner Wright for extending the courtesy of a telephonic interview with Applicants on May 12, 2004 in connection with the above-identified application.

During the telephonic interview, Examiner Wright agreed to reconsider the outstanding rejection under 35 U.S.C. § 102(b) over STN International CAPLUS Database, Accession No. 1989:1851777 to Showalter *et al.* ("Showalter Abstract"). Applicants explained why the rejected claims are not anticipated by the cited art regardless of whether or not the Showalter Abstract discloses the compound anthra[1,9-cd]pyrazol-6(2H)-one. In addition, Applicants briefly referred to the evidence of record from Chemical Abstracts Services ("CAS") which rebuts the Examiner's interpretation of the Showalter Abstract. The Examiner agreed to reconsider the remarks and amendments set forth in the Reply to Final Office Action Under 37 C.F.R. § 1.113 filed in the United States Patent and Trademark

Office ("USPTO") on March 15, 2004 in connection with the above-identified application and the letter from CAS submitted concurrently therewith. Accordingly, Applicants submit the following documents concurrently with the filing of a Request for Continued Examination Under 37 C.F.R. § 1.114 (with provision for the required fee):

(1) a copy of a Reply to Final Office Action Under 37 C.F.R. § 1.113 (attached hereto as **Exhibit 1**) filed in the USPTO on March 15, 2004 in connection with the above-identified application; and

(2) a copy of a letter from CAS, including Exhibits A-E, (attached hereto as **Exhibit 2**) filed in the USPTO on March 15, 2004 concurrently with the above-referenced Reply to Final Office Action Under 37 C.F.R. § 1.113.

Applicants respectfully submit that all of the pending claims are allowable and that the rejection under 35 U.S.C. § 102(b) over the Showalter Abstract must be withdrawn. If the Examiner still disagrees, as discussed during the interview she is invited to call the undersigned to schedule an additional telephonic interview or personal interview to resolve any remaining concerns.

It is believed that no fee is due in connection with this Supplemental Reply; however, in the event any fee is required, please charge the required fee to Jones Day Deposit Account No. 503013.

Respectfully submitted,

Anthony M. Insogna, Reg. No. 35,203

Date: May 13, 2004

By: Michael D. Burns, Reg. No. 47,458 35,203

Anthony M. Insogna (Reg. No.)

JONES DAY
222 East 41st Street
New York, New York 10017
(212) 326-3939

Express Mail No.: EV 335 859 265 US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Bennett et al.	Confirmation No.: 6892
Application No.: 09/642,557	Group Art Unit: 1626
Filed: August 18, 2000	Examiner: Wright, S.
For: PYRAZOLOANTHRONE AND DERIVATIVES THEREOF AS JNK INHIBITORS AND COMPOSITIONS AND METHODS RELATED THERETO	Attorney Docket No.: 10624-046-999

REPLY TO FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.113

Commissioner for Patents
P.O. Box 1450
Mail Stop AF
Alexandria, VA 22313-1450

Sir:

In response to the Final Office Action mailed October 16, 2003, please enter the following amendments and consider the following remarks intended to place this application into form for allowance. Applicants submit herewith: (a) an Amendment Fee Transmittal with provision for the required fee (in duplicate); (b) a Petition for Extension of Time two (2) months from January 16, 2004 up to and including March 16, 2004 Under 37 C.F.R. 1.136(a) with provision for the required fee (in duplicate); and (c) a Notice of Appeal with provision for the required fee (in duplicate).

Amendments to the claims are reflected in the listing of claims which begins on page 2 of this paper.

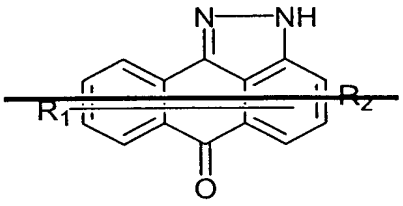
Remarks begin on page 16 of this paper.

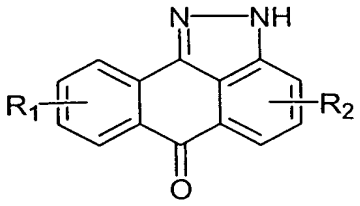
Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims

1. (Currently Amended) A compound having the structure:

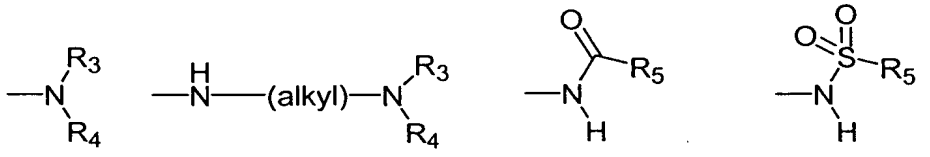




or a pharmaceutically acceptable salt thereof,

wherein

R_1 and R_2 are optional substituents that are the same or different and independently represent nitro, trifluoromethyl, sulfonyl, aryl, arylalkyloxy, arylalkyl, cycloalkylalkyloxy, cycloalkyloxy, alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono- or di-alkylaminoalkoxy, or a group represented by formula (a), (b), (c) or (d):



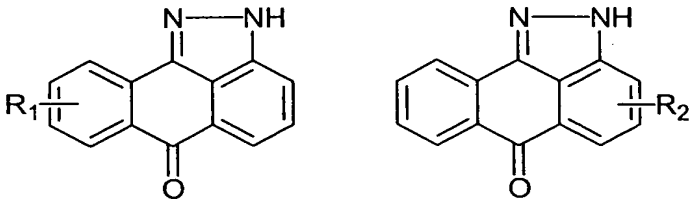
(a) (b) (c) (d)

R_3 and R_4 are the same or different and independently represent cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, alkoxyamino, or alkoxy(mono- or di-alkylamino); and

R_5 represents hydrogen, alkyl, cycloalkyl, carbocyclic aromatic, heterocyclic aromatic, arylalkyl, cycloalkylalkyl, alkoxy, amino, mono- or di-alkylamino, arylamino, arylalkylamino, cycloalkylamino or cycloalkylalkylamino, with the proviso that carbocyclic aromatic is not phenyl;

and with the proviso that at least R_1 or R_2 is present.

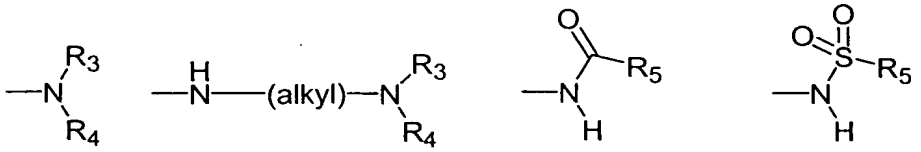
2. (Previously Presented) A compound having one of the following structures:



or a pharmaceutically acceptable salt thereof,

wherein

R_1 represents nitro, trifluoromethyl, sulfonyl, carboxyl, alkoxycarbonyl, aryl, arylalkyloxy, arylalkyl, cycloalkylalkyloxy, cycloalkyloxy, alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono- or di-alkylaminoalkoxy, or a group represented by formula (a), (b), (c) or (d):

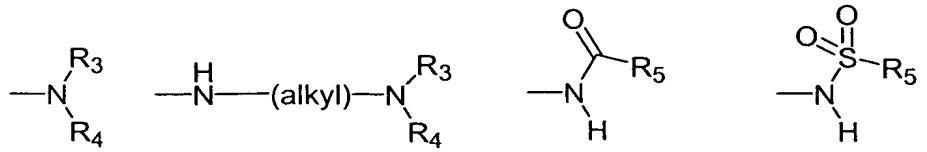


(a) (b) (c) (d)

when R_1 is present, R_3 and R_4 are the same or different and independently represent hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, alkoxyamino, or alkoxy(mono- or di-alkylamino);

when R_1 is present, R_5 represents hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, alkoxy, amino, mono- or di-alkylamino, arylamino, arylalkylamino, cycloalkylamino or cycloalkylalkylamino;

R_2 represents nitro, trifluoromethyl, sulfonyl, alkoxycarbonyl, aryl, arylalkyloxy, arylalkyl, cycloalkylalkyloxy, cycloalkyloxy, alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono- or di-alkylaminoalkoxy, or a group represented by formula (a), (b), (c) or (d):

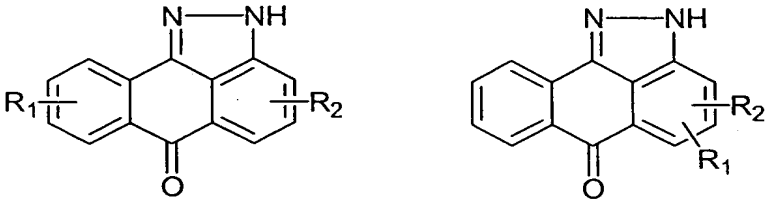


(a) (b) (c) (d)

when R_2 is present, R_3 and R_4 are the same or different and independently represent cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, alkoxyamino, or alkoxy(mono- or di-alkylamino); and

when R_2 is present, R_5 represents hydrogen, alkyl, cycloalkyl, carbocyclic aromatic, heterocyclic aromatic, arylalkyl, cycloalkylalkyl, alkoxy, amino, mono- or di-alkylamino, arylamino, arylalkylamino, cycloalkylamino or cycloalkylalkylamino with the proviso that carbocyclic aromatic is not phenyl.

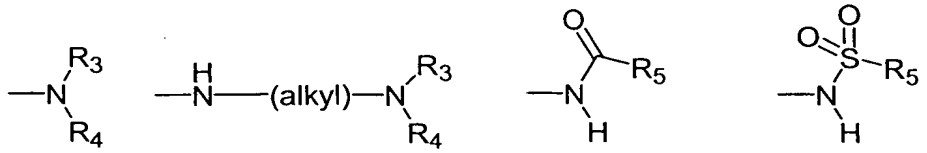
3. (Currently Amended) A compound having one of the following structures:



or a pharmaceutically acceptable salt thereof,

wherein

R_1 and R_2 <u>independently</u> represent alkyl, halogen, nitro, trifluoromethyl, carboxyl, alkoxycarbonyl, alkoxy, aryl, aryloxy, arylalkyloxy, arylalkyl, cycloalkylalkyloxy, cycloalkyloxy, alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono- or di-alkylaminoalkoxy, or a group represented by formula (a), (b), (c) or (d):

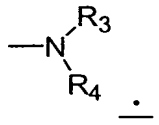


(a) (b) (c) (d)

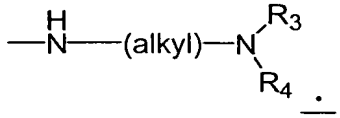
~~R_3 and R_4 taken together represent alkylidene or a heteroatom-containing alkylidene, or~~ R_3 and R_4 are the same or different and independently represent hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, alkoxyamino, or alkoxy(mono- or di-alkylamino); and

R_5 represents hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, alkoxy, amino, mono- or di-alkylamino, arylamino, arylalkylamino, cycloalkylamino or cycloalkylalkylamino.

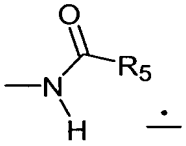
4. (Currently Amended) The compound of claim 2 wherein R_1 and R_2 are:



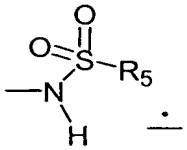
5. (Currently Amended) The compound of claim 2 wherein R_1 and R_2 are:



6. (Currently Amended) The compound of claim 2 wherein R_1 and R_2 are:



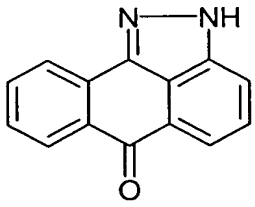
7. (Currently Amended) The compound of claim 2 wherein R_1 and R_2 are:



8. (Previously Presented) A composition comprising the compound or pharmaceutically acceptable salt of the compound of claim 1 and a pharmaceutically acceptable carrier.

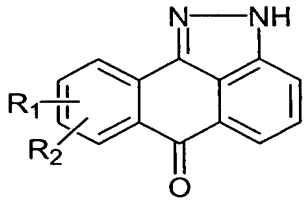
9-23. (Canceled)

24. (Currently Amended) A pharmaceutical composition comprising a compound having the structure:



or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

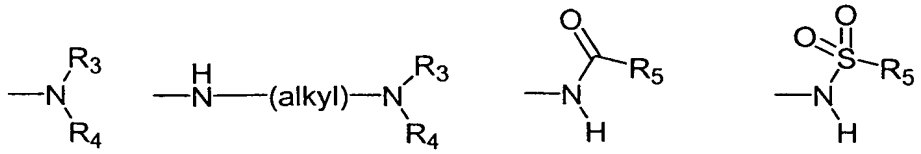
25. (Previously Presented) A compound having the structure:



or a pharmaceutically acceptable salt thereof,

wherein

R_1 and R_2 are optional substituents that are the same or different and independently represent, nitro, trifluoromethyl, sulfonyl, carboxyl, alkoxycarbonyl, aryl, arylalkyloxy, arylalkyl, cycloalkylalkyloxy, cycloalkyloxy, alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono- or di-alkylaminoalkoxy, or a group represented by formula (a), (b), (c) or (d):



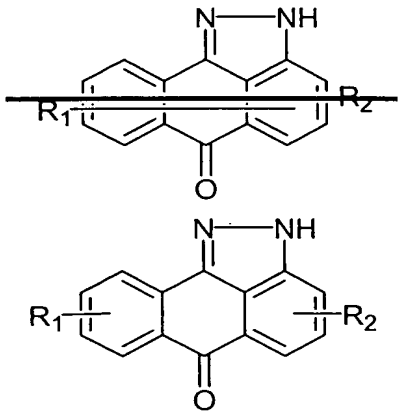
(a) (b) (c) (d)

R_3 and R_4 are the same or different and independently represent hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, alkoxyamino, or alkoxy(mono- or di-alkylamino); and

R_5 represents hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, alkoxy, amino, mono- or di-alkylamino, arylamino, arylalkylamino, cycloalkylamino or cycloalkylalkylamino;

and with the proviso that at least one of R_1 or R_2 is present.

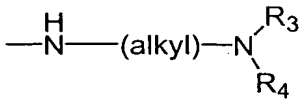
26. (Currently Amended) A compound having the structure:



or a pharmaceutically acceptable salt thereof,

wherein

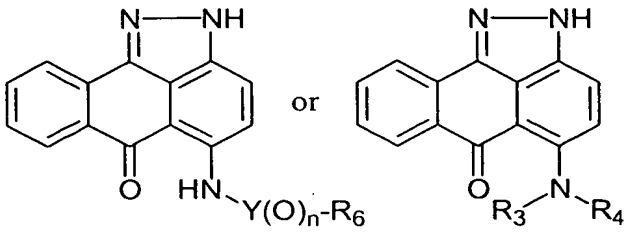
R_1 and R_2 are optional substituents that are the same or different and independently represent:



wherein R_3 and R_4 are the same or different and independently represent hydrogen, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, alkoxyamino, or alkoxy(mono- or di-alkylamino);

and with the proviso that at least R_1 or R_2 is present.

27. (Previously Presented) A compound having one of the following structures:



or a pharmaceutically acceptable salt thereof,

wherein

Y is C or S;

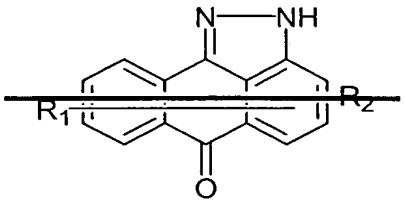
n is 1 when Y is C;

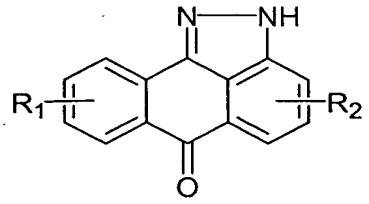
n is 2 when Y is S;

R_3 and R_4 are the same or different and independently represent alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, alkoxyamino, or alkoxy(mono- or di-alkylamino); and

R_6 represents phenyl, pyridinyl, thienyl or alkyl.

28. (Currently Amended) A method for treating a condition, comprising administering to a patient in need thereof an effective amount of a compound having the structure:

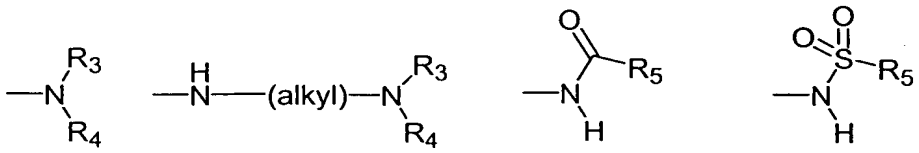




or a pharmaceutically acceptable salt thereof,

wherein

R_1 and R_2 are optional substituents that are the same or different and independently represent alkyl, halogen, nitro, trifluoromethyl, sulfonyl, carboxyl, alkoxycarbonyl, alkoxy, aryl, aryloxy, arylalkyloxy, arylalkyl, cycloalkylalkyloxy, cycloalkyloxy, alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono- or di-alkylaminoalkoxy, or a group represented by formula (a), (b), (c) or (d):



(a) (b) (c) (d)

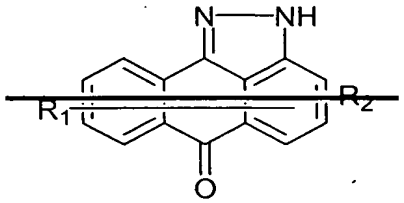
R_3 and R_4 are the same or different and independently represent hydrogen, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, alkoxyamino, or alkoxy(mono- or di-alkylamino); and

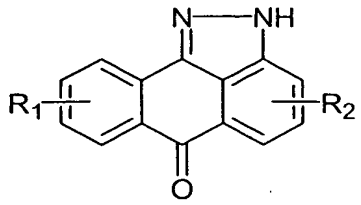
R_5 represents hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, alkoxy, amino, mono- or di-alkylamino, arylamino, arylalkylamino, cycloalkylamino, or cycloalkylalkylamino,

~~the~~ wherein said condition ~~being~~ is cancer; rheumatoid arthritis; rheumatoid spondylitis; osteoarthritis; gout; asthma; bronchitis; cystic fibrosis; inflammatory bowel disease; irritable bowel syndrome; mucous colitis; ulcerative colitis; Crohn's disease; gastritis; esophagitis; hepatitis; multiple sclerosis; endotoxin shock; psoriasis; eczema; dermatitis; atherosclerosis; restenosis following angioplasty; left ventricular hypertrophy; myocardial infarction; stroke or ischemic damage to the heart, kidney, liver, or brain; transplant rejection; or a central or peripheral neurological degenerative disorder.

29. (Previously Presented) The method of claim 28, wherein the central or peripheral neurological degenerative disorder is epilepsy, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic laterial sclerosis, a peripheral neuropathy or spinal cord damage.

30. (Currently Amended) A method for inhibiting JNK in a cell capable of expressing JNK, comprising contacting said cell with an effective amount of a compound having the structure:

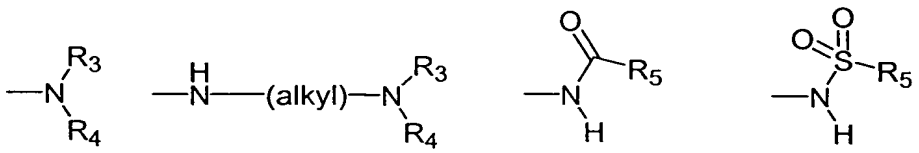




or a pharmaceutically acceptable salt thereof,

wherein

R_1 and R_2 are optional substituents that are the same or different and independently represent alkyl, halogen, nitro, trifluoromethyl, sulfonyl, carboxyl, alkoxycarbonyl, alkoxy, aryl, aryloxy, arylalkyloxy, arylalkyl, cycloalkylalkyloxy, cycloalkyloxy, alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono- or di-alkylaminoalkoxy, or a group represented by formula (a), (b), (c) or (d):

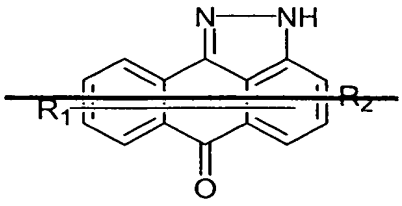


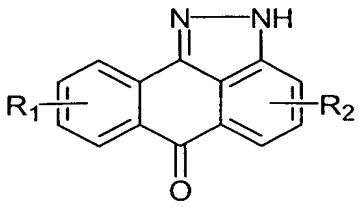
(a) (b) (c) (d)

R_3 and R_4 are the same or different and independently represent hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, alkoxyamino, or alkoxy(mono- or di-alkylamino); and

R_5 represents hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, alkoxy, amino, mono- or di-alkylamino, arylamino, arylalkylamino, cycloalkylamino, or cycloalkylalkylamino.

31. (Currently Amended) A method for inhibiting JNK, comprising contacting JNK with an effective amount of a compound having the structure:

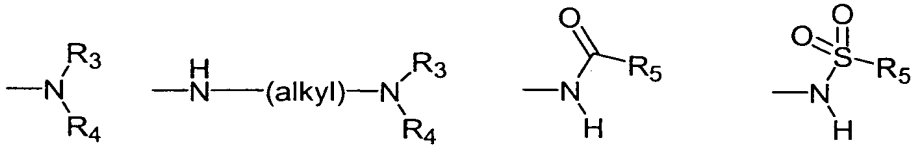




or a pharmaceutically acceptable salt thereof,

wherein

R_1 and R_2 are optional substituents that are the same or different and independently represent alkyl, halogen, nitro, trifluoromethyl, sulfonyl, carboxyl, alkoxycarbonyl, alkoxy, aryl, aryloxy, arylalkyloxy, arylalkyl, cycloalkylalkyloxy, cycloalkyloxy, alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono- or di-alkylaminoalkoxy, or a group represented by formula (a), (b), (c) or (d):



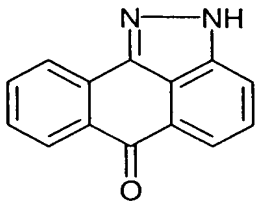
(a) (b) (c) (d)

R_3 and R_4 are the same or different and independently represent hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, alkoxyamino, or alkoxy(mono- or di-alkylamino); and

R_5 represents hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, alkoxy, amino, mono- or di-alkylamino, arylamino, arylalkylamino, cycloalkylamino, or cycloalkylalkylamino.

32. (Previously Presented) The method of claim 30 or 31, wherein the JNK is JNK1, JNK2 or JNK3.

33. (Previously Presented) The method of claim 28, 30 or 31, wherein the compound has the structure:



or a pharmaceutically acceptable salt thereof.

34. (Currently Amended) The composition of claim 8 ~~or 24~~, wherein the composition is a pharmaceutical composition.

35. (Currently Amended) The composition of claim 8 ~~or 24~~, wherein the compound or pharmaceutically acceptable salt of the compound is present in an amount that is effective for inhibiting JNK.

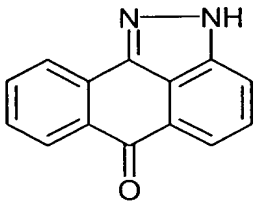
36. (Currently Amended) The composition of claim 8 ~~or 24~~, wherein the compound or pharmaceutically acceptable salt of the compound is present in an amount that is effective for treating cancer; rheumatoid arthritis; rheumatoid spondylitis; osteoarthritis; gout; asthma; bronchitis; cystic fibrosis; inflammatory bowel disease; irritable bowel syndrome; mucous colitis; ulcerative colitis; Crohn's disease; gastritis; esophagitis; hepatitis; multiple sclerosis; endotoxin shock; psoriasis; eczema; dermatitis; atherosclerosis; restenosis following angioplasty; left ventricular hypertrophy; myocardial infarction; stroke or ischemic damage to the heart, kidney, liver, or brain; transplant rejection; or a central or peripheral neurological degenerative disorder.

37. (Previously Presented) The composition of claim 36, wherein the central or peripheral neurological degenerative disorder is epilepsy, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic laterial sclerosis, a peripheral neuropathy or spinal cord damage.

38. (Currently Amended) The composition of claim 24 or 34, wherein the composition is in the form of a pill, tablet or capsule.

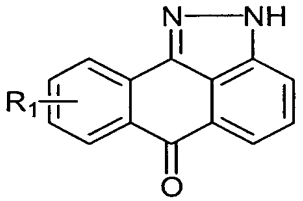
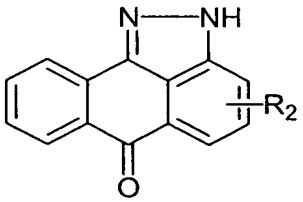
39. (Canceled)

40. (Currently Amended) The method of claim 28 wherein ~~R_1 and R_2 are not present, and~~ the compound ~~having the following structure~~ is:



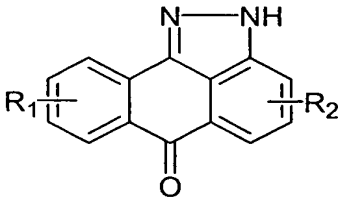
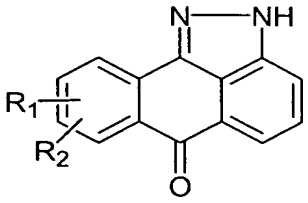
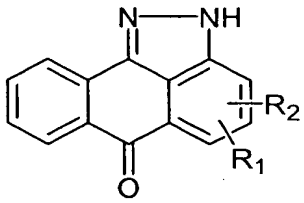
or a pharmaceutically acceptable salt thereof.

41. (Currently Amended) The method of claim 28 wherein R_1 or R_2 is present, and the compound ~~having~~ has one of the following structures:

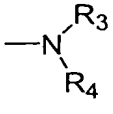
or a pharmaceutically acceptable salt thereof.

42. (Currently Amended) The method of claim 28 wherein both R_1 and R_2 are present, and the compound ~~having~~ has one of the following structures:

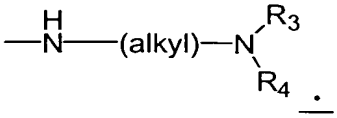




or a pharmaceutically acceptable salt thereof.

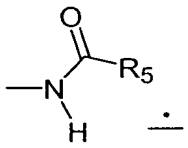
43. (Currently Amended) The method of claim 42 wherein R_1 and R_2 are:



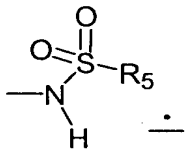
44. (Currently Amended) The method of claim 42 wherein R_1 and R_2 are:



45. (Currently Amended) The method of claim 42 wherein R_1 and R_2 are:



46. (Currently Amended) The method of claim 42 wherein R_1 and R_2 are:



47. (New) The composition of claim 24 or 34, wherein the composition is suitable for oral administration.

48. (New) The composition of claim 24 or 34, wherein the composition is suitable for parenteral administration.

49. (New) The composition of claim 24 or 34, wherein the compound is present in an amount from 0.1 mg to 250 mg per dosage.

50. (New) The composition of claim 24 or 34, wherein the compound is present in an amount from 1 mg to 60 mg per dosage.

51. (New) A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt of the compound of claim 2 and a pharmaceutically acceptable carrier.

52. (New) A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt of the compound of claim 3 and a pharmaceutically acceptable carrier.

53. (New) A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt of the compound of claim 25 and a pharmaceutically acceptable carrier.

54. (New) A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt of the compound of claim 26 and a pharmaceutically acceptable carrier.

REMARKS

Claims 1-8 and 24-38 and 40-54 are presently pending. Applicants gratefully acknowledge the Examiner's indication that claims 1, 2, 4-8, 25, 26 and 30-32 are allowable over the art of record.

Claims 1, 3-7, 24, 26, 28, 30, 31, 34-36, 38 and 40-46 have been amended to more particularly point out and distinctly claim the present invention.

Claims 1, 26, 28, 30 and 31 have been amended to more clearly set forth the structure of the compounds recited therein. Support for these amendments is found at page 11, lines 15-20 of the Specification as filed. Claim 28 has been further amended to more clearly set forth the conditions recited therein.

Claim 3 has been amended to recite subject matter within the scope of the embodiment identified for examination as suggested by the Examiner.

Claims 4-7 and 43-46 have been amended to add a period at the end of each claim.

Claim 24 has been amended to recite a "pharmaceutical" composition. Support for this amendment is found at page 22, lines 19-20 of the Specification as filed.

Claims 34-36 have been amended to no longer depend from claim 24.

Claim 38 has been amended to further depend from claim 24. Support for this amendment is found at page 23, lines 27-28 of the Specification as filed.

Claims 40-42 have been amended to more clearly set forth the claimed invention.

New claims 47-50 which depend from claim 24 have been added. Support for new claims 47 and 48 is found at page 23, lines 24-27 of the Specification as filed and support for new claims 49 and 50 is found at page 22, lines 25-27 of the Specification as filed.

New claims 51-54 have been added to recite pharmaceutical compositions comprising a compound of claims 2, 3, 25 and 26, respectively. Support for new claims 51-54 is found at page 22, lines 19-20 of the Specification as filed. No new matter has been added.

Claim 39 has been canceled without prejudice for being drawn to non-elected subject matter. Applicants reserve their right to prosecute the subject matter of any canceled claim, any amended claim or any other unclaimed subject matter in one or more divisional, continuation or continuation-in-part applications.

I. The Withdrawal of Claim 39

The Examiner has indicated that the rejection of claim 39 under 35 U.S.C. § 112, second paragraph, has been withdrawn. However, the Examiner has further indicated that claim 39 has been withdrawn from consideration and restricted out due to the classification of JNK. In response to the restriction, Applicants have canceled claim 39 without prejudice. Applicants reserve their right to prosecute the subject matter of claim 39 in one or more divisional, continuation or continuation-in-part applications.

II. Objections to Claims 3, 27, 29, 37, 38 and 41-46

Claims 3, 27, 29, 37, 38 and 41-46 have been objected to.

Claim 3 has been objected to for allegedly containing subject matter outside of the scope of the embodiment identified for examination. Claim 3 has been amended to recite subject matter within the scope of the embodiment identified for examination.

Claim 27 has been objected to for allegedly containing subject matter outside of the scope of the embodiment identified for examination. Applicants respectfully disagree that claim 27 contains subject matter outside of the scope of the embodiment identified for examination. The first structure of claim 27 is that where R_1 is -NH-$Y(O)_n$-R_6 and R_2 is absent. This class of compounds is encompassed by claim 1. In particular, when Y is C and n is 1, the compounds of claim 27 are encompassed by claim 1 wherein R_1 is (c) -NH-C(O)-R_5 and R_2 is absent, and when Y is S and n is 2, the compounds of claim 27 are those of claim 1 wherein R_1 is (d) -NH-$S(O)_2$-R_5 and R_2 is absent. The second structure of claim 27 is that where R_1 is -NR_3R_4 and R_2 is absent. This class of compounds is also encompassed by claim 1. In particular, these compounds are the compounds of claim 1 wherein R_1 is (a) -NR_3R_4 and R_2 is absent. Thus, Applicants believe that the subject matter recited by claim 27 is that which was identified for examination.

Claims 43-46 have been objected to for missing periods at the end of each claim. Claims 43-46 have been amended to add a period at the end of each claim. Claims 4-7 have also been amended to add a period at the end of each claim.

Claims 29, 41 and 42, each of which depends from claim 28, have been objected to as being dependent upon a rejected base claim. In view of the below arguments with respect to claim 28, Applicants believe that claim 28 is now in condition for allowance and that the objection to claims 29, 41 and 42 has been overcome.

Claims 37 and 38, each of which depends from a claim which is dependent upon claim 24, have been objected to as being dependent upon a rejected base claim. Claim 37 no longer depends from a claim which is dependent upon claim 24. Furthermore, in view of the below arguments with respect to claim 24, Applicants believe that claim 24 is now in condition for allowance. Accordingly, Applicants believe that the objection to claims 37 and 38 has been overcome.

In view of the above amendments and remarks, Applicants believe that the objections to claims 3, 27, 29, 37, 38 and 41-46 cannot stand and must be withdrawn.

III. The Rejection Under 35 U.S.C. § 102(b)

The sole art rejection is against claims 24, 28, 33-36 and 40 which remain rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by STN International CAPLUS Database, Accession No. 1989:1851777 to Showalter *et al.* (the "Showalter Abstract"). The Examiner alleges, as a result of her STN search, that the Showalter Abstract discloses anthra[1,9-cd]pyrazol-6(2H)-one as an anti-cancer drug. Applicants respectfully traverse for the reasons set forth below.

First, Applicants recognize that the compound in question was known prior to their invention, although not as a biologically active material and not through any disclosure in the Showalter Abstract. Second, the underlying full publication of the Showalter Abstract (*i.e.*, Showalter *et. al. Bioactiv. Mol. 6*:201-243 (1988)) itself, and thus the CAS abstract describing it, do not disclose anything about the compound anthra[1,9-cd]pyrazol-6(2H)-one, much less that it is an anti-cancer agent. This fact is demonstrated by the letter and underlying evidence provided by CAS itself, which letter accompanies this response. As the Examiner will see, CAS agrees with Applicants that the Showalter Abstract does not disclose the compound anthra[1,9-cd]pyrazol-6(2H)-one but merely discloses derivatives thereof (*see* January 15, 2004 letter from CAS and accompanying Exhibits A-E enclosed herewith).

Accordingly, Applicants respectfully submit in view of the above arguments and documentation from CAS that the Showalter Abstract does not in fact disclose anthra[1,9-cd]pyrazol-6(2H)-one and, thus, cannot anticipate the present claims.

Furthermore, Applicants submit that even assuming *arguendo* that the Showalter Abstract did disclose anthra[1,9-cd]pyrazol-6(2H)-one itself, the Showalter Abstract still does not anticipate the present claims because the Showalter Abstract does not teach each and

every limitation of the present claims as is required for a reference to be anticipatory. *In re Paulson* 30 F.3d 1475, 1478 (Fed. Cir. 1994).

In particular, the Showalter Abstract does not teach any pharmaceutical use for anthra[1,9-cd]pyrazol-6(2H)-one itself. In contrast, the Showalter Abstract only teaches the anti-tumor effects of *derivatives* of anthra[1,9-cd]pyrazol-6(2H)-one. Nowhere in the Showalter Abstract is it disclosed that there is a pharmaceutical use for anthra[1,9-cd]pyrazol-6(2H)-one itself. The absence of any data or discussion of the biological activity of this compound in the Showalter Abstract and the fact that the underlying publication teaches only derivatives in and of itself *teaches away* from the compound as an anti-cancer agent.

Thus, the Showalter Abstract fails to teach each and every limitation of the pharmaceutical composition claims and the method of use claims which relate to anthra[1,9-cd]pyrazol-6(2H)-one.

Accordingly, in view of the above, Applicants respectfully submit that the rejection of claims 24, 28, 33-36 and 40 under 35 U.S.C. § 102(b) over the Showalter Abstract cannot stand and must be withdrawn.

IV. Conclusion

Applicants respectfully submit that all of the pending claims are allowable. If the Examiner still disagrees, she is invited to call the undersigned to schedule an interview to resolve any remaining concerns.

It is believed that no fee other than that for the extension of time is due in connection with this Reply; however, in the event any additional fee is required, please charge the required fee to Jones Day Deposit Account No. 503013.

Respectfully submitted,

Anthony M. Insogna, Reg. No. 35,203

By: Michael L. Brun, Reg. No. 47,458 35,203

Date March 15, 2004

Anthony M. Insogna (Reg. No.)

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